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Review Article

CURRENT CHALLENGES IN THE DEVELOPMENT AND FORMULATION OF AMORPHOUS SOLIDS

Gannu Praveen Kumar[1]*, Bakka Sravan Kumar[2]

[1]Department of Industrial Pharmacy
St. Peter's Institute of Pharmaceutical Sciences
2-4-1211, Vidyanagar
Hanamkonda, Warangal, India
[2]Talla Pamavathi college of Pharmacy, Orus, Kareemabad, Warangal (AP) India – 506012

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*Corresponding author
Gannu Praveen Kumar

Email:
ghalo2010@gmail.com

ABSTRACT

Interest in amorphous pharmaceutical systems is steadily growing over the last 10 years. The amorphous state is critical in determining the solid state, physical and chemical properties of many pharmaceutical dosage forms. The main reason of the growing interest toward amorphous materials is the need to improve the bioavailability of drugs with poor aqueous solubility. Many drugs exist in crystalline solid form due to reasons of stability and ease of handling during the various stages of drug development. Conversion of the crystalline to amorphous form may occur during various pharmaceutical processes. This could change the dissolution rate and transport characteristics of the drug. The current focus of research in this area is to understand the origins of amorphous forms. The various thermodynamic phenomena such as glass transition, fragility, molecular mobility, devitrification kinetics, molecular level chemical interactions, solubility and stability are critically discussed. The aim of this review is to understand the recent development in the area of amorphous state and to address the current challenges faced by pharmaceutical formulation and process development scientists and thus is mandatory to anticipate future developments.

Key words: Crystalline solids, amorphous forms, characterization, stabilization.

INTRODUCTION

Amorphous forms, by definition, are the distinct class of solids, separated from the more common and well-known crystalline solids. At the molecular level, they lack the three-dimensional long-range order. Instead, their molecules are randomly arranged in space and the interactions between neighboring molecules are not repeated (Morris *et al.*, 2001). Their structure can be thought of as being similar to that of a frozen liquid with the thermal fluctuations present in a liquid frozen out, leaving only "static" structural disorder (Elliot *et al.*, 1986). Amorphous state is characterized by randomly arranged molecules, of which the motions are kinetically frozen, at least on experimental time scales. A little provocation by different stressors can accelerate the mobility of molecules and facilitate the achievement of most stable and ordered crystalline states. These issues gain greater importance during pharmaceutical manufacturing processes, wherein a solid experiences the variable extent of stress (Gupta *et al.*, 2004). Solubility of a given solid is a sum of crystal packing energy, cavitation and solvation energy. Amorphous state exists due to the absence of an ordered crystal lattice which requires minimal energy thus providing the maximal solubility advantage as compared to the crystalline and hydrated forms of a drug as shown in figure 1. (Gupta *et al.*, 2004).

Crystalline and amorphous states of a solid exhibit altered molecular interactions (Tang *et al.*, 2002) which may pose as energy barriers for phase transformations. These structural changes depend on adjustment in the nearest neighbor relationships, including parameters such as intermolecular distances and patterns in hydrogen bonding (Brittain 2002). The process can be envisioned as decrease in configurational entropy with a simultaneous increase in the number of molecules constituting cooperatively rearranging regions, favoring a gain in molecular order. Interest in amorphous pharmaceutical systems has been steadily growing over the last 10 years. But the current interest has been raised by major

developments like growing attention to pharmaceutical solids in general, especially polymorphs and solvates (Zhou *et al.*, 2002; Bhugra *et al.*, 2006) and a revived interest in the science of glasses and the glass transition (Angell 1996).

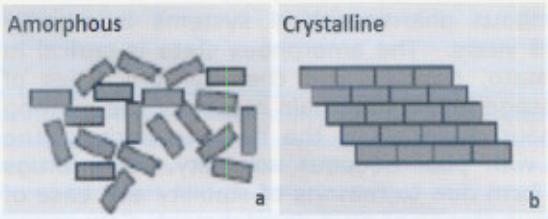

Figure 1. a) Amorphous arrangement; b) Crystalline arrangement

Screening for amorphous materials

In recent years, several amorphous active pharmaceutical ingredients (APIs) have been marketed as drug products. Some of them which include are Accolate (zafirlukast), Ceftin (cefuroxime axetil), and Accupril (quinapril hydrochloride). Lilly's Humulin L contains both amorphous and crystalline insulin to provide immediate and long-term effects. An amorphous material can be substantially more soluble than the corresponding crystalline material, as much as 1600 times more soluble according to a recent publication (Hancock, 2000). In some cases, this increased solubility leads to enhanced bioavailability. Because of these potential benefits, solid form screening should encompass a search for both crystalline and amorphous forms. This application note suggests a strategy for finding the best amorphous form early in drug development, using small amounts of material, with the overall goal of reducing the time to launch. Three main steps involved in the development strategy are assessment of the API solubility, and the second is screening for amorphous forms and the third step is determination of the stability of amorphous forms (Byrn *et al.*, 1995). The goal of a micro amorphous screen is to prepare amorphous forms on the micro scale using a variety of methods. Solid State Chemical Information (SSCI), a division of Aptuit provides comprehensive cGMP solid state chemistry research and analytical services to the pharmaceutical industry. SSCI help with many different aspects of solid form screening. Methods used at SSCI include flash evaporation, lyophilization, and quench cooling of the melt. Such procedures are performed at scales that provide about 0.1 to 5 mg of each sample. If larger amounts of material are available, grinding experiments at ambient or liquid nitrogen temperatures are carried out. Samples are analyzed by x-ray powder diffraction (XRPD), followed by other techniques as needed. Estimation of the solubility and stability of amorphous material prepared in the screen can also be accomplished using the small, initially formed samples. SSCI uses several technologies for carrying out microscale reactions. One is SSCI's patented capillary crystallization technology, which provides very high supersaturation levels through simple evaporation experiments, establishing conditions conducive to the formation of solid forms ranging from the most stable to higher free energy solids to very unstable forms. Amorphous materials are not as thermodynamically stable as their crystalline counterparts, and thus are commonly found using the capillary method. Samples generated in capillaries can be analyzed in situ by XRPD, optical microscopy, Raman spectroscopy, and differential scanning calorimetry. The small amount of sample necessary for generation and analysis of a solid in a capillary (0.05 to 1 mg) makes this technology ideal for micro screening (Chyall *et al.*, 2002).

Methods of forming an amorphous sample

Amorphous substances can be classified as "strong" and "fragile" glass formers. Due to some kinetic and thermodynamic reasons, preparation of amorphous solids is easy and direct for good glass formers and difficult for poor glass formers i.e fragile glass formers (Lian, 2001).

Separation / precipitation of solid from liquid

The methods included using this principle is as follows.

Spray drying

In recent years, drug substances with poor aqueous solubility have become increasingly common, presenting formulators with a considerable number of extra challenges.

One emerging technology that has gained something of a reputation for offering a relatively straightforward solution to these problems is the solid dispersion technique. This involves molecular or colloidal dispersions of amorphous compounds, which are scientifically proven to dissolve more easily than crystalline forms. The evidence suggests that formulations containing amorphous active pharmaceutical ingredients (APIs) present enormous potential in overcoming problems of limited bioavailability of poorly-soluble APIs.

Scientists have in the past been somewhat reluctant to adopt this principle, largely because of concerns over stability and issues relating to limited shelf life. But more recently, it has been shown that properly formulated solid dispersions actually offer long-term stability, thus removing a key barrier to evaluating the technology. They can either be prepared by melt extrusion or spray-drying, but the advantages of the latter allow formulators to choose from a wide selection of polymers, solvents and adjuvants. In recent Contract Pharma analysis, spray-drying was pinpointed as an "excellent" manufacturing option when working with temperature-sensitive solutions. This is because the spray-drying process involves relatively low temperatures and only limited contact with the hot processing gas.

Generally speaking, the use of spray-drying to manufacture solid dispersions is a relatively simple process. First of all, the drug substance is dissolved in a solvent system together with a polymer dispersant system and any other necessary adjuvants to form the spray-drying feed solution that will be used. Next, this is pumped into the top of the spray-dryer, along with nitrogen, or another heated gas, before being atomised into fine droplets. As the droplets descend through the drying chamber, the solvent is quickly removed, leaving a dry power with distinct properties. This powder can then be collected in a cyclone and secondarily dried to remove residual solvents in accordance with guidelines from the International Conference on Harmonisation (ICH).

"One of the advantages of spray-drying is its ability to control powder characteristics which can have a tremendous impact on secondary formulation and manufacturing of tablets or capsules. This is where expertise and a strong understanding of the fundamentals of spray-drying can define success or failure of a solid dispersion,". Careful selection of spray-drying equipment and parameters, such as inlet/outlet temperatures and feed solution variables, allow various powder characteristics, from particle size and distribution to dispersability and flow can all be efficiently controlled.

Particularly important is the evaluation of inlet, outlet and condenser temperatures, which allows the engineer to design highly-efficient and reproducible spray-drying processes. Mr Ross noted that parameters such as bulk density, flowability and residual solvent levels are all highly impacted by the temperatures. "For example, spray-drying at lower outlet temperatures will produce a powder with greater bulk density but a higher residual solvent level. Although most spray-dried solid dispersions will require some level of secondary drying, residual solvent levels of the powder must be evaluated as they can have a significant impact on the short term, and thereby long-term physical stability," he added. Finally, it is important for evaluation to be conducted to establish the extent to which outlet temperatures impact the physical stability of the amorphous powder, as well as other properties that may influence secondary dosage development.

Spray drying often results in physical transformation i.e., it leads to conversion of a crystalline phase to an amorphous state, because the amorphous state is metastable with respect to the crystalline form. Spray-drying was performed using a laboratory scale spray dryer under the standard set of conditions like drug solution concentration, inlet and outlet temperature, feed rate, drying air flow rate and atomization air pressure (Jeong-Soo, 2008). The amorphous materials being in a thermo-dynamically metastable state, are susceptible to reconversion to the crystalline state and affects many physicochemical characterization of the drug (Jacob, 2011).

Solidification from the melt

Although this technique is not used in the large scale production of pharmaceutical products, this technique is often employed on

the laboratory scale as a first approach to prepare the amorphous phase of a compound. The advanced techniques for preparing amorphous solids span the range of quenching rates. These techniques are not fundamentally different from those used for preparing crystalline solids (Fig.1). The point is simply that care is taken to quench fast enough to form the glass rather than slow enough to form the crystal. For materials with very high glass-forming tendency, the melt can be allowed to cool slowly by simply turning off the furnace or by bringing it down in a programmed manner (Fig1.1a). Typical cooling rates are in the range from 10^{-4} to $10^{-1°}$ K/sec.

Somewhat faster rates are needed to quench a glass such as amorphous selenium, an elemental glass composed of long-chain polymeric molecules. Using an ice-water bath to quench modest volumes of the melt, yields rates in the range 10^{1}- $10^{2°}$ K/sec (Fig1.1b). Se glass can be prepared by this method. This metallic glass has a glass-forming tendency high enough to allow it to be prepared in bulk form, rather than the thin-film form characteristic of other metallic glasses. There are other techniques also for the melt-quenching methods developed specifically for metallic glasses. These methods are collectively called splat-quenching techniques (Fig1.1c), and achieve T values in the range 105-108°K/sec (Zallen, 1998).

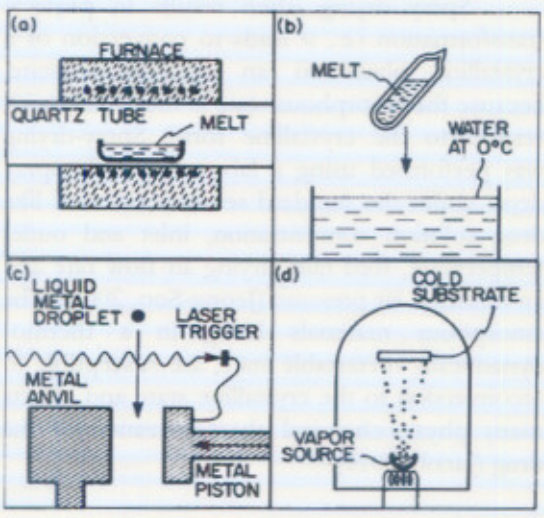

Figure 2. a) slow cooling; b) moderate quenching; c) rapid splat quenching; d) condensation from the gas phase.

Freeze drying

In a freeze drying process, rapid freezing favors the formation of an amorphous solute, whereas introducing an annealing step may promote crystallization (Pikal, 1994). Lyophilization is highly limiting in its scope when applied to organic small molecules with poor aqueous solubility. Although lyophilization can be performed with organic solvents, it is not a preferred technique since complete removal of solvent from the system may be challenging (Nagapudi *et al.,* 2008).

Mechanical disruption of an ordered structure

Milling

It is a Process that introduce mechanical or chemical stress (e.g., grinding, milling and wet granulation) which can render crystalline materials fully or partially amorphous.

Dehydration

Dehydration of crystalline hydrates has been demonstrated as a feasible and "gentle" route to the amorphous state of organic solids. Saleki Gerhardt *et al.,* showed that heating the crystalline raffinose pentahydrate at 60°C in vacuum converts the material to an amorphous form (Saleki-Gerhardt *et al.,* 1995).

Preparation methods are found to influence the solubility, as well as physical and chemical stability of amorphous drugs. Zhang *et al.,* (2009) investigated physical and chemical stability of the Quench-cooled amorphous simvastatin and cryo-milled amorphous simvastatin and revealed that the solubility of amorphous forms prepared by both methods was enhanced compared to the crystalline form. The amorphous substances have many useful properties like higher solubility, dissolution rate, and better compression characteristics than corresponding crystals. The amorphous solids are generally less stable physically and chemically than corresponding crystals (Vogel *et al.,* 1921).

Characterization of amorphous materials

The key to understanding the properties of the amorphous state is recognized by the fact that molecules in this state can exhibit significant molecular motion over timescales of pharmaceutical interest both above and below

the glass transition temperature (T_g). The glass transition temperature is where an amorphous substance changes from a super-cooled liquid with relatively low viscosity to an unstable glass with much greater viscosity. Motion in the form of translational and rotational diffusion, which is essential for any physical or chemical process, can generally be described in terms of temperature, viscosity, and molecular size. It can occur in seconds at and above T_g to months or years below T_g. In some cases amorphous materials can be produced by mixing solids so that molecular dispersions result. The dispersions will have properties distinct from those of the individual components. Molecular dispersions are important in pharmaceutical situations such as: stability in sugar-protein lyophilized and spray dried products, dissolution of orally administered drug-polymer dispersions, crystallization in transdermal patches, mechanical characteristics of plasticizer-polymer film coating systems and process-induced drug excipient interactions. There are a variety of physical techniques utilized for characterizing amorphous solids. X-ray powder diffraction measurements are used to confirm the crystalline or amorphous nature of the starting materials. As shown in figure 3, it is used to determine if any change in their form occurred as a result of their testing.

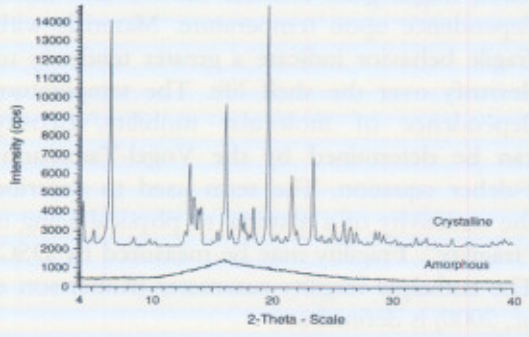

Figure 3. X-ray diffraction patterns for powdered amorphous and crystalline samples of an experimental drug substance (Hancock *et al.*, 2002).

Differential scanning calorimetry (DSC) is the most widely used thermal analytical technique applied to the characterization of amorphous solid dispersions. It measures the rate of heat flow to measure the heat of transition. As all transitions in materials involve flow of heat (into the sample in endothermic events and out of the sample for exothermic events) DSC is the universal detector for measuring the wide variety of transitions in pharmaceutical materials (Jared *et al.*, 2011). Other important techniques include Scanning electron microscopy, Isothermal calorimetry, Dielectric analysis, Dynamic Mechanical Analysis, Dilatometry and thermal stimulating current.

The structure of amorphous solids is usually described as possessing crystals like short range molecular rearrangement, but lacking long range order. If crystallization is avoided, many liquids of pharmaceutical relevance vitrify at a temperature (Tg) approximately 2/3 to 4/5 of the crystalline melting point, Tm. Modulated DSC and can be used to separate reversing and non-reversing components at a glass transition (e.g., in a spray dried lactose), a beneficial utility in the assignment of glass transitions that are weak or overlap with other thermal events. Apart from quench cooling, a melt miscible impurity may be introduced to inhibit crystallization. Crystallization of carbohydrates and derivatives, which are common pharmaceutical excipients, presents a special challenge. Xylitol, for instance, is crystallized initially as a more stable polymorph, with the metastable form being impossible to make again.

Properties of amorphous materials

Some of the important properties that include are Amorphous particles appear dark under polarized light microscope, typically exhibit a significant initial increase in aqueous solubility and dissolution rate relative to the crystalline material, True density of the amorphous form is 5–20% less than the crystalline form, X-rays are randomly diffracted by amorphous powders resulting in a broad halo for the diffraction pattern (Figure. 4) (Crocker *et al.*, 1997) and water vapor is sorbed by amorphous samples in large and non-stoichiometric amountsrelative to crystalline samples (Zografi *et al.*, 1994). The tendency for amorphous materials to sorb significant amounts of water vapor from their surrounddings (Figure 4) can give markedly reduced chemical and physical stability relative to the crystalline form of the material.

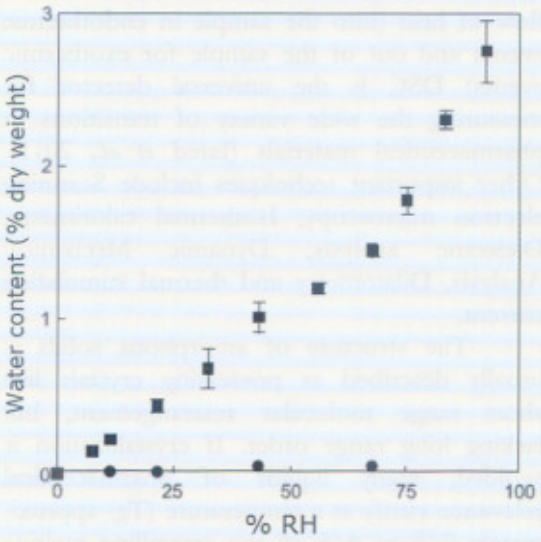

Figure 4. Water vapor sorption isotherm for crystalline and amorphous samples of indomethacin (■) Amorphous; (●) crystalline (Andronis *et al.*, 1997)

Limitations of amorphous systems such as physical instability and higher chemical reactivity, act as a hurdle in their extensive commercialization. Thereby, it is important to understand the molecular and thermodynamic properties that contribute to the solubility and stability of amorphous drugs. Thermodynamically, the amorphous form is characterized by presence of 'excess' enthalpy, specific volume, entropy and free energy. The properties of these characterized materials are as follows.

Glass transition temperature

Glass transition temperature is the characteristic property of amorphous materials. There has been a constant debate over glass transition being a kinetic or a thermodynamic phenomenon. The thermodynamic viewpoint suggests that as T_g is associated with a change in the derivative of extensive thermodynamic properties such as volume, enthalpy, entropy and heat capacity, the glass transition is a second-order thermodynamic phase transition. The T_g is also thought to be a "thermodynamic necessity" to prevent the "entropy crisis" of the non crystalline state. In contrast, the kinetic view point explains the observed structural changes as the consequence of a dynamic transition in the relaxation of the super cooled liquid, which is not associated with any abrupt changes in thermodynamic parameter. The glass transition event in kinetic terms is based on relaxation times. The "structural relaxation time" is defined as the time taken by the molecule to diffuse from the centre of its vibration to another centre across intermolecular distance. T_g is defined as the temperature at which mean relaxation time (t) changes by two to three orders of magnitude and equals the time of observation (t_0). T_g is a kinetic parameter and is observed to vary with temperature scanning rate and thermal history (Weuts *et al.*, 2003).

Fragility

Amorphous substances can be classified as "strong" and "fragile" glass formers based on the temperature dependence of mean relaxation time (or viscosity) above T_g depicted by the Angell's plot. Strong glass formers show an Arrhenius type relationship with activation energy independent of temperature. At the molecular level, strong glass formers exhibit an open network structure, with a built-in resistance to structural change with increasing temperature. Thus strong glasses exhibit small change in heat capacity at T_g. On the other hand, fragile glass formers show a non linear dependence upon temperature. Materials with fragile behavior indicate a greater tendency to devitrify over the shelf life. The temperature dependence of molecular mobility/viscosity can be determined by the Vogel-Tammann-Fulcher equation. The term used to describe the sensitivity of a material to physical aging is "fragility". Fragility may be measured by DSC. The enthalpic fragility parameter (Robertson *et al.*, 2000) is defined as

$$m_{\Delta h} = -(d \log \beta_c)/(d(T_{f,ref}/T_f))$$

$m_{\Delta h}$ is the fragility parameter,
β_c is the perior cooling rate,
T_f is the fictive temperature measured in heating
$T_{f,ref}$ is the reference fictive temperature

Molecular mobility

Molecular mobility of amorphous pharmaceuticals is a key factor in determining their stability, reactivity, and physicochemical properties. Crystallization is a process that involves two separate but interdependent steps: nucleation followed by crystal growth. It is important to note that both these steps require diffusion or rearrangement of molecules either to form agregates of molecules leading to stable nuclei or to attach to a growing crystal face, thus one of the key attributes that govern the physical stability of an amorphous glass or supercooled liquid is molecular mobility (Hancock *et al.,* 1995) . Likewise, chemical reactivity also depends on some level of molecular mobility (Yoshioka *et al.,* 2007). In addition to the excess thermodynamic properties described previously, the amorphous state also has excess volume or "free volume" in relation to the equilibrium crystalline state, and even though the amorphous glass exhibits solid-like behavior below Tg, there is sufficient free volume that molecular motions leading to molecular rearrangements can occur (Hancock *et al.,* 1997). Over time these molecular rearrangements can manifest as either relaxation of the amorphous glass to a lower free energy state or formation of stable nuclei, leading to devitrification of the glass to a more stable crystalline state. There are numerous reports describing crystallization of amorphous materials following storage at temperatures below Tg (Alig *et al.,* 1997; Bhugra *et al.,* 2008; Yoshioka *et al.,* 2004) and nucleation has been reported at temperatures as low as 55°C below Tg (Hancock *et al.,* 1995). Consequently there is intense interest in being able to predict physical stability by understanding and measuring molecular mobility; however, as will be discussed, this is an extremely challenging undertaking. This is in part due to the strong dependence of molecular mobility on temperature, as discussed in more detail below.

Temperature dependence of relaxation process

As the temperature of an undercooled liquid approaches the glass transition (T_g), the viscosity increases, the free volume in the system decreases, and the time for a molecule to diffuse an interparticulate distance or the structural relaxation time increases. Both structural relaxation and viscosity of a material exhibit strong temperature dependences (Figure 5), with relaxation times on the order of 100s at Tg compared to hours and days at temperatures below Tg, while viscosity can vary from > 10^{12} Pas below Tg to 10^{-4} Pas at the melting temperature (Hancock *et al.,* 1999).

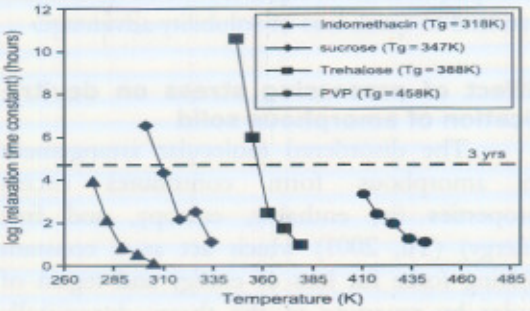

Figure 5. Temperature dependence of average molecular relaxation times (Hancock, 2002)

Devitrification kinetics

The rate and mechanism of devitrification of amorphous solid is material specific and dependent on environmental conditions (temperature, pressure, and/or humidity) encountered during processing of solid dosage forms (Gupta *et al.,* 2005).

Effect of humidity

The higher hygroscopicity of the amorphous system is usually higher in comparison to the crystalline drug which further enhance devitrification. Typically, crystalline materials adsorb vapors in smaller quantities at their surface. In contrast, amorphous systems absorb vapors in relatively large amounts (even up to 100 % by weight) (Yoshioka *et al.,* 2007). It has been shown that even a small amount of amorphous material, embedded within a largely crystalline matrix, preferentially absorbs water vapor. This amplifies the local water content and a corresponding plasticization of the amorphous structure (Ahlneck *et al.,* 1990; Gupta *et al.,* 2004). Thus, relative humidity is an important factor influencing the solid-state properties of glassy systems. Water acts as a potential plasticizer that increases the free volume conducive to greater molecular motions favoring devitrification. Storage of amorphous

celecoxib at 25°C and a range of humidity conditions (0%, 35%, 60%, and 80% RH) are found to result in complete devitrification. Storage at high humidities resulted in 100% crystallization in <3 days, whereas 0% RH could sustain the crystallization by allowing 80% crystallization in 75 days. Thus, exposure to humidity favored crystallization of amorphous solid. A rapid rate of devitrification can lead to quick loss of solubility advantage.

Effect of processing stress on devitrification of amorphous solid

The disordered molecular arrangement in amorphous form contributes excess properties (ie, enthalpy, entropy, and free energy) (Yu, 2001) which act as a constant driving force for loss of energy and regain of order by reverting to the thermodynamically stable crystalline form. The dissipation of this energy could be enhanced to a variable extent in the presence of different stress-inducers. Manufacturing of a solid dosage form involves various unit operations, like size reduction (mechanical and thermal stress), drying (thermal stress), blending (mechanical stress), granulation (mechanical and humidity stress), compression (mechanical and thermal stress), coating (thermal and humidity stress), and so forth, which can provide sufficient inputs for reducing the energy gap between the metastable amorphous and stable crystalline form. The behavior of amorphous solid in the presence of these processing stresses would allow for adoption of suitable measures in the designing of amorphous systems that can be advantageously used. To eliminate the small crystalline fractions retained during preparation of amorphous solid, inclusion of high Tg additives can provide benefit in terms of reduction of molecular motions within the experimental time frame. This goal can be achieved with the use of poly(vinyl pyrrolidone), (Dmitri, *et al.,* 2007) which provides stability to amorphous solid during storage, as well as dissolution.

Molecular interactions in crystalline and amorphous state

The amorphous state differs from the crystalline state in the molecular level arrangements. The low molecular weight organics such as pharmaceutical materials show extensive hydrogen bonding, complex molecular geometry and conformational flexibility, which together define the ease of glass formation and its subsequent stability. Spectroscopic techniques that are used to study inter and intra molecular hydrogen bonding, structural shape, steric hindrance and inter-conversion between conformational isomers, can explain the glass formation and their physical stability. These differences in interactions manifest as different macroscopic properties of the crystalline and amorphous state (Yu, 2001).

Thermodynamics of amorphous materials

Amorphous systems have been known to demonstrate an 'excess' of thermodynamic properties (enthalpy, entropy, and free energy) relative to their crystalline counterparts. On the one hand, these 'excess' properties bestow enhanced solubility, improved bioavailability and better compressibility, however, on the other hand, they are responsible for their physical instability by way of devitrification. Compared to the crystalline form of a drug, the amorphous form is in a state of higher energy. This is due to the fact that the amorphous state possesses excess thermodynamic properties such as enthalpy, entropy and Gibbs free energy. The relationship of the thermodynamic properties and temperature for the amorphous and crystalline state is shown in figure 1 As a liquid melt of a crystal is cooled rapidly, recrystallisation may be prevented and the slope of the equilibrium liquid line may be followed below the melting temperature, T_m, resulting in a gradual decrease of thermodynamic properties below T_m. This is the super-cooled liquid state, in which viscosity is low (typically around $10^{-3} - 10^{12}$ Pa s) and mobility of the molecules is high and they are able to follow any further decrease of temperature to attain equilibrium conditions. However, upon further cooling, at the glass transition temperature (T_g), the molecules cannot follow the decrease in temperature any longer and the system solidifies, falling out of equilibrium. This is represented by the change of the slope in Figure 1.5. Below the T_g, the system is in the glassy state, exhibiting high viscosities of $> 10^{12}$ Pas.

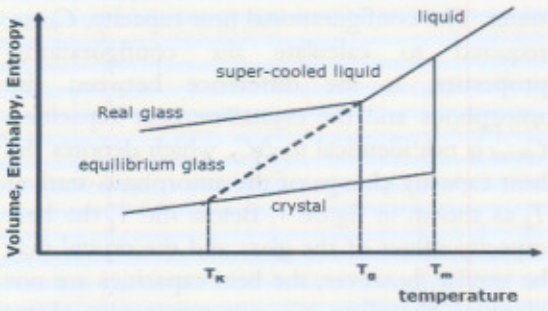

Figure 6. Thermodynamic relationship of crystalline and amorphous state as a function of temperature (Hancock *et al.,* 1997)

If the T_g did not occur and the system remained in equilibrium throughout the cooling process, the super-cooled liquid line would be followed (now as an equilibrium glass) and it would intersect the crystal line at the Kauzmann temperature, T_K. Below the T_K, the amorphous system would have lower entropy and enthalpy than the crystalline state, which presents a violation of the laws of thermodynamics. Therefore, the occurrence of the T_g has two implications for amorphous systems. Firstly glasses are in a non-equilibrium state and equilibrium thermodynamics cannot be applied below that temperature and secondly the physico-chemical properties of amorphous systems above and below the T_g are different. During storage, it is often observed that the amorphous state reduces its excess enthalpy and entropy without recrystallising. This is called "relaxation" as the amorphous state relaxes towards a lower energetic state, still remaining in the amorphous form. The real glass relaxes asymptotically towards the equilibrium glassy state. This relaxation behaviour can be seen as an indication that below the T_g mobility is low, but still existent. The higher energetic state is beneficial in terms of improving the solubility of a compound. However, it is detrimental to the physical stability (Hilden *et al.,* 2004; Yu 2001). Due to the enhanced thermodynamic properties of the amorphous state compared to the crystalline state, recrystallisation provides a means of reducing this excess free energy but in DO Ing so, the solubility advantages are negated. Crystallisation is a result of a nucleation process, where stable nuclei are created, followed by crystal growth. The recrystallisation of an amorphous form is governed by the same factors as the crystallization from a melt (Hancock *et al.,* 1997) and therefore the crystallisation processes have been described on the basis of the classical nucleation theory (CNT) for homogenous nucleation (Schmelzer 200841). Nucleation is a process which involves the overcoming of a potential barrier and is first described by Gibbs (Longley, 1948). The change of Gibbs free energy (ΔG), due to the formation of a cluster of the new phase (crystal) is given by equation 1:

$$\Delta G = \Delta G_V + \Delta G_S \quad \text{.....(1)}$$

ΔG_S is the change in surface free energy (in J mol^{-1}) and ΔG_V is the volume free energy change (in J mol^{-1}). The value of ΔG_S is associated with the formation of the cluster and represents a positive quantity.

The value of ΔG_V is associated with the phase transition of liquid to solid and represents a negative quantity (Rodriguez-Hornedo *et al.,* 1999). According to the CNT, when nucleation occurs, clusters grow and decay until a stable nucleus is formed. After a cluster of a critical size has been formed, it will grow in size and hence recrystallisation of the amorphous form takes place. Nucleation and crystal growth are not solely governed by thermodynamics but also require individual molecules to move via diffusion. This kinetic proportion of the recrystallisation effect is usually considered as the molecular mobility or its reciprocal, the relaxation time. It has long been suggested that molecules exhibit sufficient mobility only at temperatures close to or above the T_g, and storage at temperatures below T_g would ensure physical stability. It has however been found that nucleation and crystal growth also occur at temperatures well below the T_g, however, the relative rate may be much slower than in the temperature region above the T_g (Bhugra *et al.,* 2008; Yoshioka,1994). Recrystal-lisation should therefore be influenced by thermodynamic (such as enthalpy, entropy and Gibbs free energy) and kinetic parameters (such as mobility). A commonality of the thermody-namic and kinetic parameters is the involve-ment of the configurational entropy (S_{conf}) which is the difference in entropy between the amorphous and the crystalline state.

Thermodynamic involvement of S_{conf}

The desired properties of the amorphous state (higher solubility and dissolution rate compared to the crystalline form) have been attributed, at least in part, to an increase in thermodynamic properties, e.g., free energy, entropy and enthalpy. This change in free energy is regarded as a driving factor for recrystallization. The larger the difference in free energy between the amorphous and crystalline state the more thermodynamically favorable the situation will be upon recrystallisation. The difference in Gibbs free energy between the amorphous and the crystalline states can be calculated using enthalpic and entropic values for the amorphous and crystalline state as tated below:

$$G_{conf} = H_{conf}(T) + S_{conf}(T) \quad \text{.....(2)}$$

The term "configurational" denotes the difference between the amorphous and the crystalline state and the parameters H_{conf} and S_{conf} may be calculated from their relationship with the heat capacity.

$$H_{conf}(T) = H^{amorph}(T) - H^{crystal}(T) \quad \text{.....(3)}$$

$$S_{conf}(T) = S^{amorph}(T) - S^{crystal}(T) \quad \text{.....(4)}$$

$$H_{conf} = \Delta H_m + \int_{T_m}^{T} Cp_{conf} dT \quad \text{.....(5)}$$

$$S_{conf} = \Delta S_m + \int_{T_m}^{T} \frac{Cp_{conf}}{T} dT \quad \text{.....(6)}$$

H_{conf} is the configurational enthalpy (in $Jmol^{-1}$), S_{conf} the configurational entropy (in $Jmol^{-1}K^{-1}$), ΔH_m the melting enthalpy of the crystal (in $Jmol^{-1}$) and ΔS_m the melting entropy of the crystal (in $Jmol^{-1}K^{-1}$). The melting entropy can be obtained from the following relationship:

$$\Delta S_m = \frac{\Delta H_m}{T_m} \quad \text{.....(7)}$$

The configurational thermodynamic values give an indication of the relationship between the amorphous state and the crystalline state of a compound. The larger the co figurational values are the greater are the differences between the crystalline and the amorphous states. The configurational heat capacity, C_{pconf}, required to calculate the configurational properties, is the difference between the amorphous and the crystalline heat capacities. C_{pconf} is not identical to ΔC_p, which denotes the heat capacity change of the amorphous state at T_g as shown in figure 7. Below the T_g the heat capacity values of the glass and the crystal may be similar, however, the heat capacities are not identical, therefore, C_{pconf} is never zero. After passing through the T_g the C_{pconf} of an amorphous compound may increase or decrease with temperature or follow a specific temperature dependence, depending on the properties of the material (Hodge 1996; Privalko 198045, 46). The temperature dependence of the configurational heat capacity above T_g has been described by the hyperbolic relation presented below:

$$Cp_{conf} = \frac{K}{T} = \frac{Cp_{conf}(T_g)T}{T} \quad \text{.....(8)}$$

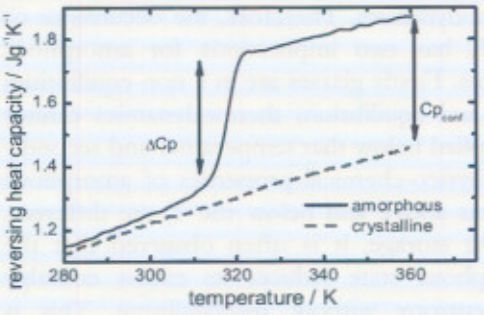

Figure 7. Heat capacity difference (ΔC_p) and configurational heat capacity (C_{pconf}) of indomethacin

Kinetic involvement of S_{conf}

The amorphous state not only possesses higher thermodynamic properties compared to the crystalline state, it also shows enhanced molecular mobility (Shamblin *et al.*, 1999) and this is considered an important factor for the subsequent physical and chemical instabilities (Tombari *et al.*, 2008). Crystal nuclei formation, the first step of the recrystallisation process, is a result of the localized faster mobility of molecules (Williams *et al.*, 1970) and degradation reactions such as hydrolysis or protein degradation have been attributed to increased molecular mobility within the amorphous state (Yoshioka *et al.*, 2007).

Molecular mobility has therefore been the topic of numerous investigations, however, due to the complex nature of the amorphous state and the still poorly understood relaxation properties, to date no single equation can be used to estimate the relaxation time of the amorphous state. Among those generally used are the Kohlrausch–Williams–Watts equation (KWW) (Williams *et al.*, 1970), the Adam-Gibbs equation (AG) (Adam *et al.*, 1950) and the Vogel–Tamman–Fulcher equation (VTF) (Fulcher 1925, 1965; Tammann *et al.*, 1926; Vogel, 1921). These equations all show advantages and disadvantages as they address different issues, but the most commonly used equation to estimate the molecular mobility for the temperature range below the T_g is the AG. The governing thought of the AG equation is that a liquid consists of regions that rearrange themselves in units, the so-called cooperatively rearranging regions (CRR). Upon cooling from the super-cooled liquid state, these CRR become progressively larger. The size of the CRR is determined by the difference in the configurational entropy, S_{conf} , of the liquid which varies with temperature. When the temperature is high, the S_{conf} is large and the size of the CRR is small. Upon cooling, the S_{conf} decreases and in return the size of the CRR increases. In the AG theory, this increasing co-operativity is believed to be due to a loss of configurational entropy, which enables the calculation of molecular mobility

$$\tau(T) = \tau_0 \exp\left(\frac{\Delta\mu s^*_{conf}}{k_B T S_{conf}(T)}\right) \quad \text{.....(9)}$$

with relaxation time below T_g (in s), τ_0 pre-exponential parameter (lifetime of the atomic vibrations, 10-14 s), $\Delta\mu$ activation energy of cooperative rearrangement (J mol^{-1}), s^*_{conf} entropy of smallest cooperative molecular region (J mol^{-1} K^{-1}), k_B Boltzmann constant (1.38 JK^{-1}) and $S_{conf}(T)$ configurational entropy at temperature T (J mol^{-1} K^{-1}).

Equation 9 simplifies to the following expression if the properties of the glass forming liquid ($\Delta\mu$ and s^*_{conf}) are considered constant:

$$\tau(T) = \tau_0 \exp\left(\frac{C}{T S_{conf}(T)}\right) \quad \text{.....(10)}$$

C is a constant.

By applying equation 10 it has to be considered that the entropic contributions are entirely due to S_{conf} and any other influence (e.g.,vibrational entropy) is neglected (Pjohari, 2001),. As a result, S_{conf} has a direct influence on the relaxation time and therefore on molecular mobility. As a glass relaxes isothermally, it reduces a portion of its excess entropy which in return leads to an increase of relaxation time. The molecular mobility of an amorphous state therefore is not only temperature dependent but also time dependent. A convenient way to express the temperature and time dependence of the molecular mobility is to introduce the fictive temperature, T_f (Figure 8).

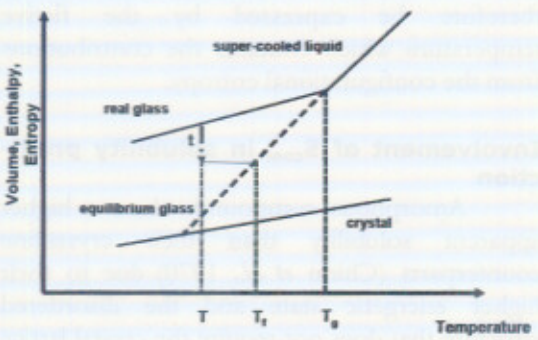

Figure 8. T is the isothermal relaxation temperature, T_f is the fictive temperature and T_g is the glass transition temperature (Kawakami *et al.*, 2005).

Relationship of enthalpy and temperature for an amorphous system

A real glass is not in equilibrium, therefore applying thermodynamic principles proves challenging. However, thermodynamics can be estimated by relating the real glass to the theoretical equilibrium glass at the same temperature. The fictive temperature is defined as the temperature at which the system under investigation has the same thermodynamic properties as its equilibrium state at that temperature and that time.

The configurational entro-py (Vogel, 1921) can therefore be descrybed by

$$S^{g}_{conf}(T) = S^{e}_{conf}(T_f) = \int_{T_0}^{T_f} \frac{Cp_{conf}}{T} dt \quad \text{.....(11)}$$

with S_g conf configurational entropy of the real glass (in J mol^{-1} K^{-1}), S^{e}_{conf} configurational entropy of the equilibrium super-cooled liquid (in J mol^{-1} K^{-1}) and T_f fictive temperature (in K). The fictive temperature is a convenient way of describing the temperature and time dependence of S_{conf} for real glasses and enables calculation of molecular mobility in these systems. Through a number of rearrangements and substitutions of S_{conf} in equation 10 (Hilden *et al.,* 2004) the AG equation 12 can be written as:

$$\tau(T) = \tau_0 \exp\left(\frac{DT_0}{T - (T/T_f)T_0}\right) \quad \text{.....(12)}$$

D is the dimensionless Angell's strength parameter and T_0 is the temperature of zero, S_{conf} (in K). The relaxation time τ may therefore be expressed by the fictive temperature which contains the contributions from the configurational entropy.

Involvement of S_{conf} in solubility prediction

Amorphous compounds show a higher apparent solubility than their crystalline counterparts (Chiou *et al.,* 1970) due to their higher energetic state and the disordered structure that does not require the crystal lattice to be broken upon dissolution. According to studies (Parks *et al.,* 1928) the theoretical solubility ratio $(\sigma^{amorph}/\sigma^{crystal})$ of the amorphous and crystalline form at a given temperature can be described through the free energy difference between the two forms (Parks *et al.,* 1928; Parks *et al.,* 1934).

$$G_{conf} = RT \ln\left(\frac{\sigma^{amorph}}{\sigma^{crystalline}}\right) \quad \text{.....(13)}$$

Gas constant R = 8:314 J mol^{-1} K^{-1}

The value of G_{conf} can be calculated as presented in equation 2, via C_{pconf} and hence S_{conf}. This approach has already been successfully applied for estimating the solubility differences between different crystalline polymorphs (Aguiar *et al.,* 1967; Grant *et al.,* 1990). In the reported literature, experimental solubility increases of up to 10 fold have been reported (Hancock *et al.,* 2000) for amorphous systems, which in return can increase the bioavailability of a poorly soluble compound considerably. However, for amorphous compounds the calculated solubility may increase by up to 1,600 fold (Chawla *et al.,* 2007). This potential increase usually is not observed in vitro and the estimated values are significantly smaller. This is partly due to the fact that the amorphous state is far from equilibrium which poses difficulties in determining their equilibrium thermodynamic properties and partly due to the tendency of the amorphous state to revert back to the crystalline state upon exposure to solvents such as water or biorelevant media (Grant *et al.,* 1990). It is also observed that the amorphous state does not recrystallise to its original crystalline state but may crystallise to a different, potentially less soluble, polymorph (Savolainen *et al.,* 2009). This is not trivial and can pose challenges during development of drug formulations. Despite their inaccurate values for absolute solubility, the estimated solubility ratios are a useful tool for estimating the theoretical maximal solubility and serve as an indication of the theoretical driving force for dissolution. These considerations regard the S_{conf} highlight the importance of this parameter in terms of amorphous stability and solubility which are the major factors of interest in pharmaceutics.

Stability of amorphous solids

The amorphous state, being a high-energy state, is usually less stable than the corresponding crystalline form. Therefore, it is important to store the amorphous material under conditions that suppress its tendency to undergo unwanted physical changes (e.g., crystallization, aggregation of proteins) and also chemical degradation over the shelf life of the product (Shamblin *et al.,* 1999).

The main challenge in working with the amorphous form of drugs is their physical instability. In order to benefit from the advantages (enhanced solubility may lead to higher bioavailability) of the amorphous form, methods of stabilizing the amorphous state against recrystallization need to be found and optimized (Andronis *et al.,* 1997; Hancock *et al.,* 1995; 2000).

Parameters used for the prediction of stability mean relaxation time constant (τ)

The molecular relaxation processes are typically non-exponential and are usually characterized using the empirical Kohlaursch-William-Watts (KWW) equation. Determination of the relaxation process at different storage conditions to determine the relaxation or aging behaviour is a means to assess the "effective age" of an amorphous raw material (Chawla *et al.,* 2009). In lieu of glass transition, molecular mobility has been quantified in terms of structural relaxation time measurements. Correlation between physical stability of the amorphous phase and relaxation time has been explored in large number of publications (Zhou *et al.,* 2002; Yoshioka *et al.,* 2001; Yoshioka *et al.,* 2004). Structural relaxa-tion time can be determined in the time domain using methods like DSC and thermal activity monitor or in the frequency domain using methods like DES, SSNMR and TSDC (Carpentier *et al.,* 2006).

Relaxation time distribution parameter (β)

β is a fitting parameter that represe-nts the breadth or skewness of the relaxa-tion time distribution. Using equation (5) the average relaxation time τ at a temperature T can be calculated. Typically materials that have long relaxation times (in order of hundreds of days to years) at the storage temperature are said to be physically stable. Such measurements can be done for either AAPI (Amorphous Active Pharmaceutical Ingredient) or ASD (Amorphous Solid Dispersion) materials (Marsac *et al.,* 2006; Marsac *et al.,* 2008) Relaxation time measurements provide an estimate for the physical stability of amorphous materials using small amounts of material and as such are useful measurements to carry out while developing the amorphous phase as a preclinical candidate. These measure-ments are carried out in dry nitrogen atmos-phere (~ 0% RH) in DSC and consequently do not shed any light on the effect of moisture on crystallization. It is well known that moisture acts as a plasticizer and reduces glass transition temperature and thereby can have a profound impact on glass transition and the dynamics associated with glass transition.

Temperature characteristic parameters (enthalpy and entropy) and crystallization rate constant (*k*)

The amorphous samples are annealed at various temperatures below glass transition temperaturefor different lengths of time. For each time period the enthalpic recovery is measured. From the enthalpic recovery the fraction of glass relaxed Φ(t) can be calculated using:

$$\phi(t,T) = \frac{\Delta H_t(T)}{\Delta H_\infty(T)}$$

$\Delta H_t(T)$ is the enthalpic recovery at time t and temperature T. ΔH_∞ is the maximum enthalpic recovery at the temperature T. ΔH_∞ can be calculated using:

$$\Delta H_\infty = \Delta C_p(T_g - T) \quad (4)$$

ΔC_p is the heat capacity change across glass transition that is observed at the start of the experiment and Tg is the glass transition temperature. Recent studies have been reported where crystal nucleation has been found to occur at temperatures well below the glass transition temperature. It is believed that at temperatures in the range of T_g-40° c, the beta relaxation is the dominant relaxation mechanism. As opposed to glass transition (alpha relaxation), the beta relaxation is associated with high frequency small length-scale molecular motions. Examples of such localized motions include rotations of methyl groups and ring flips in benzene groups. Such motions well below Tg could lead to spontaneous formation of crystal nuclei thereby generating physical instability in the amorphous phase. Based on these observations it has been argued that, if the storage temperature is well below Tg, then beta relaxation process must be characterized (as it is the dominant relaxation process) to make meaningful inferences of amorphous stability. The beta process can be directly observed and activation energies can be calculated when DES and TSDC techniques are used (Shmeis *et al.,* 2004). If the activation barrier is high, then the probability of nucleation is considered low. Recently Vyazovkin (Shmeis *et al.,* 2004) have employed DSC to study the beta relaxation in indomethacin (Vyazovkin *et al.,* 2007; Vyazovkin *et al.,* 2006). In this study the beta relaxation manifests itself as an endothermic

peak below glass transition. By investigating the scanning rate dependence of the temperature location of beta transition, the authors are able to calculate the activation energy of the beta relaxation. Beta relaxation is an event associated with low heats and as such DSC may not be the best method to investigate it. The commonly used method of storing drugs at or below their Kauzmann temperature (T_k) [which is usually estimated to be 50 K below their glass transition temperature (T_g)] is governed by the principle that at sufficiently low temperatures, molecular mobility practically ceases. However, the 'T_g–50 K rule of thumb' does not guarantee sufficient stability over the desired shelf-life, as recrystallization has been observed for a number of drugs at temperatures well below T_g. The factors governing recrystallization still are poorly understood, but thermodynamic and kinetic parameters are thought to influence stability. Kirsten A Graeser, *et al.,* (2010) assessed the configurational properties of some amorphous drugs to predict the physical stability using acetaminophen, cefuroxime axetil, donepezil HCl, fenofibrate, griseofulvin, ibuprofen, indomethacin, lacidipine, nifedipine, simvastatin, tolbutamide and troglitazone drugs and conc for the configurational entropy and hence the solubility ratios.

Stabilization of amorphous solids

The stabilization of amorphous solids is multifaceted which includes physical and chemical aspects:

Physical aspects

Stabilization of labile molecules

Freezing and drying are essential steps in the preparation of protein and peptide formulations (Pikal, 1994) and in the preservation of organisms (Crowe, *et al.,* 1998). It has been observed that the peptides and organisms can be effectively protected against freezing and drying damages when they are co-processed with certain excipients, typi cally carbohydrates and derivatives (sucrose, trehal-poly(vinylpyrrolidone) and poly(vinylpyrroli-done- ose, mannitol, sorbitol, etc.) (Carpenter, 1994; Sun *et al.,* 1998) .

Protection against crystallization of excipients

It is generally accepted that in order to act as stabilizers, an excipient must mix homogeneously with the drug to be stabilized. However certain excipients (e.g., mannitol) have strong tendency to stabilizing crystallize, leading to phase separation and loss of stabilizing power. Crystallization can also lead to the formation of slow dissolving particles, causing slow reconstitution of parenteral products.

Vitrification

Vitrification based stabilization relies on immobilization and isolation of labile substances. In vitrification based stabilization strategies, Tg provides a concrete guide to the selection of stabilizers and storage temperatures. By eliminating plasticizers and introducing antiplasticizers one can increase T_g and reduces structural mobility.

Chemical aspects

The prevention of chemical degradation and microbial growth by the use of anti-oxidants, pH, buffer and preservatives is very critical in pharmaceutical processing of amorphous solids.

Prime approaches of stabilization

Storge at T_g - 50K temperature conditions

At temperature T_0 or T_g-50K the molecular mobility is lowered and thus the reversion process is limited. This approach is less widely accepted as providing such temperature conditions during pharmaceutical processing, handling and storage is not feasible.

Antiplasticization approach

When the amorphous drug is dispersed in a carrier (antiplastcizer) matrix which has a higher T_g value, the net glass transition of miscible matrix is elevated, thus the molecular mobility of the drug is reduced. This is called the antiplasticization effect and can be predicted by the Gordan Taylor equation. Selection of high molecular weight carrier with high T_g value and a high carrier:drug ratio can

Table I. Marketed preparations of amorphous solids

Product	Compound (s)	BCS Class	Dipersion Manufacture	Dipersion Polymer	Dipersion Process	Max Dose (m|gA)	Dosage Form
Kaletra	Lopinavir / Ritonavir	IV	Abbot	PVP/VA	Melt extrusion	200/50	
Intelence	Etravirine	IV	Tibotec/Jhonson & Jhonson	HPMC	Spray drying	100	
Sporanox	Itraconozole	II	Janssem/Orto McNell	HPMC	Spray layering	100	460mg, 800mg, tablet capsules
Rezulin[1]	Troglitazone	II	Pfizer (Parke Davis)	PVC	Melt extrusion	400	tablet
	Torcetrapib2	II	Pfizer	HPMCAS	Spray drying	60	<1g, tablet>

further reduce the molecular mobility of the amorphous drug. For amorphous drugs, solid dispersions provide maximum stability benefit when the drug is molecularly dispersed in the carrier matrix. This also provides the solubility advantage as on dissolution of solid solution the drug is presented as a supersaturated solution or precipitated as fine colloidal particles or oil globule in submicron size. The commonly used antiplasticizers are the hydrophilic organic polymers such as polyvinylpyrrolidone, polyethylene glycol and various cellulose derivatives like hydroxypropyl-methylcellulose, hydroxypropylcellulose etc.

Interactions

Specific reversible chemical interactions such as electrostatic bonds, vander waal forces and H-bonding between drug and carrier can limit the molecular mobility of drug in amorphous state. The preferential interaction between drug and carrier can retard the self association of drug molecules thus inhibit the crystallization process and contribute to the enhanced amorphous state solubility and stability.

Pharmaceutical applications of amorphous solids

Amorphous solids have a plethora of applications in the development of various dosage forms and it is evident from table I that the availability of market preparations of amorphous solids for clinical benefit. The importance of use of amorphous drugs in solid dosage forms are as follows.

Dissolution enhancement

They are used in the development of solid dispersions since rapid disintegration and dispersion occur from the dosage form. Onoue *et al.,* (2009) developed novel amorphous solid dispersion respirable powder of CsA for pulmonary administration. In their findings, it is reported that the dissolution is improved after intratracheal administration with 71 and 85% reduction of granulocyte recruitment in broncho alveolar lavage fluids and lung tissues, respectively, in rats (Onoue *et al.,* 2009).

Improvement of flow properties

Spray dried dispersion powders can be developed with improved flow. Hirofumi Takeuchi *et al.,* (2005) prepared amorphous solid dispersion particles of Indomethacin (IMC) with non-porous (Aerosil 200) and porous silica (Sylysia 350) by using spray-drying method. Dissolution property of IMC is remarkably improved by formulating the silica particles to the solid dispersion particles. The dissolution rate of IMC from solid dispersion with Sylysia 350 is rapid than that of Aerosil 200 irrespective of IMC content and are stable at 40°C, 75% RH for 2 months (Hirofumi Takeuchi *et al.,* 2005).

Stability enhancement

Hot melt extruded dispersion particles can be developed with improved compressibility and dissolution. Preparation of amorphous solid dispersions using hot-melt extrusion process of poorly water soluble compounds which degrade on melting remains a challenge due to exposure to high temperatures. Indrajit *et al.,* (2011) developed a physically and chemically stable amorphous solid dispersion with enhanced dissolution of a poorly water-soluble compound, NVS981 (using HPMC of three different grades) which is highly thermal sensitive and degrades upon melting at 165°C.

Bioavailability enhancement

Amorphous solid dispersions can be developed to improve exposure (increased bioavailability, more rapid onset, decrease dose), to support toxicology studies, as a clinical tool, to reduce variability and to decrease fed/fasted effects. Onoue *et al.,* (2010) developed amorphous solid dispersion (SD) formulations of cyclosporine A (CsA) for improving the oral bioavailability of CsA. After the oral administration of HPC based SD, enhanced CsA exposure is observed with increase in Cmax and AUC of 5-fold. The amorphous SD approach using wet-milling technology is a promosing approach to enhan-ced bioavailability leading to an improved ther-apeutic potential of CsA.

CONCLUSION

The use of amorphous pharmaceutical materials is widely considered an effective way of improving favourable drug properties. Amorphous systems are an effective strategy in the pharmaceutical dosage form development and its importance is growing further due to the increasing number of insoluble molecules being pushed into the drug development pipeline. Physical instability due to devitrifica-tion and chemical degradation are the major setbacks impeding their commercialize-tion. There are important considerations to make when formulating an amorphous substance. "An amorphous state is an interesting formulation opportunity for poorly soluble drugs. That means when solubility is very limited in the crystalline state.

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